UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,114	11/13/2001	Raymond H. Boutin	AHP1CUSA	5743

38199 7590 12/08/2003

HOWSON AND HOWSON
CATHY A. KODROFF
ONE SPRING HOUSE CORPORATE CENTER
BOX 457
SPRING HOUSE, PA 19477

EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,114	BOUTIN, RAYMOND H.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *10-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 17-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's election of group III, claim 3 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-9 and 17-48 are examined in this office action with regards to the election of claim 3.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 and 17-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to methods for the nuclear transfer of a nucleic acid composition to cells comprising introducing a multifunctional molecular complex to cells where the complex comprises a nucleic acid encoding a therapeutic protein or polypeptide and a transfer moiety.

Claims 1-9 and 17-48 are rejected under 35 U.S.C 112, first paragraph, because the specification, while being enabling for methods for the transfer of a nucleic acid composition to cells in culture comprising introducing a multifunctional molecular complex to cells where the complex comprises a nucleic acid encoding a therapeutic protein or polypeptide and a transfer moiety, does not reasonably provide enablement to methods for the nuclear transfer of a nucleic acid composition to cells in vivo comprising introducing a multifunctional molecular complex to cells where the complex comprises a nucleic acid encoding a therapeutic protein or polypeptide and a transfer moiety.

The examiner would agree that the claims are enabled for methods of transfer where the target cells are cultured cells. However, the examiner does not find the claimed methods

are enabled for methods of transfer where the target cells are contained with a body or in vivo. The in vivo aspect of claims 1-9 and 17-48 is interpreted as gene therapy as the specification does not disclose a use for delivering a therapeutic protein other than for therapeutic purposes (see specification, page 3, lines 9-13; page 39, lines 15-19 and 24-32; and page 40, line 34 to page 41, line 2).

As applicant has broadly disclosed treatment of any disease and emphasized hyperproliferative diseases, but stated no specific diseases, the examiner believes that the general teachings in the art of gene therapy and cancer gene therapy at the time of filing are appropriate in summarizing the state of the art at the time of effective filing date, September 28, 1994.

Fundamentally, the art taught that gene therapy was unpredictable without some parameters being given for achieving effective treatment. In particular, articles summarizing the state of gene therapy stated that expression and delivery of the gene desired for treatment were seen as the hurdles yet to be overcome (Blau et al (1995), page 1204, col. 1-2 bridg. Sent. and page 1205, col. 1-2 bridg. Sent.). Mulligan stated that gene therapy is unpredictable and cautioned that "a number of key technical issues need to be resolved before gene therapy can be safely and effectively applied in the clinic" (Mulligan (1993), pages 926-932, see Abstract). Science News Report states that while there have been reports of convincing gene transfer and expression, there is little evidence of a therapeutic result in patients or animal models (Science (1995) 269, page 1050, col. 2, parag. 1, lines 6-15). Further, the reports stated that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (Science 269, p. 1050, col. 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (Science 269, p. 1054, col. 3). James Wilson, one skilled in the art, stated that " '{t}he actual vectors - how we're going

to practice our trade - haven't been discovered yet" (Science 269, p. 1055, col. 2). Anderson, in a review of gene therapy for genetic diseases, states that continued expression is necessary, and that vectors for gene therapy are hit or miss because many viral promoters are shut off in primary cells in vivo (Anderson (1994), page 281, col. 2, parag. 1). Thus gene therapy in general was regarded as unpredictable by the art at the time filing, and this unpredictability laid in the realm of expression and delivery of the gene.

As for cancer as a representative hyperproliferative disease, the unpredictability for the same reasons, expression and delivery of the gene of interest for therapeutic effect, was acknowledged by the art. Russell stated that gene delivery to tumors cell in vivo by direct injection of a plasmid or virus achieves a relatively low efficiency of gene delivery as the plasmid or virus can not permeate the tumor (Russell (1994), page 1165, col. 2, parag. 4, lines 3-7). Russell also states that it is improbable that plasmids or viruses would be efficiently delivered to tumors if administered intravenously (Russell (1994), page 1166, col. 1, lines 3-11). Russell states that replicating viral vectors may offer the best chance of delivering sufficient gene to tumors for effective treatment. However, Russell also states that research of replicating viruses is needed for the delivery of therapeutic genes to tumors in vivo (Russell (1994), page 1167, col. 2, parag. 1-5). Furthermore, Gutierrez et al. (1992) reviews this technology, and indicates at pages 716-717 that there are two major limitations to mammalian cell transfection. The first is a much lower efficiency of gene expression in comparison with prokaryotic systems, with considerable differences between eukaryotic cell lines. Unlike rodent cells, most primate and human cells can integrate only a small amount of foreign DNA (about 6 kilobases); as a result, only about 10-30% of clones selected for the expression of one transcription unit will also contain a second unit in intact form. The second problem is the short-lived response after successful transfection (a few months at most) regardless of the method used. We know very little about the processing

steps within the cell. Clearly, there are problems of degradation by extracellular nucleases, absorption onto and uptake into cells, transport from cytoplasm to nucleus integration into host chromosomes, mutation, the expression of non-integrated DNA, and the transcriptional control of the transgene. Gutierrez et al also stated that for somatic cell replacement therapy, many technical hurdles need to be overcome and that suitable controls for expression vectors were not known and thus the replacement gene therapy would not have direct consequences on tumors for some time (Gutierrez (1992), page 720, col. 1, parag. 1 and parag. 3, lines 1-4).

The examiner recognizes that applicant's invention is related to the use of non-viral means, cationic lipid accompanied by receptor mediated endocytosis means, for introducing DNA into a cell in vivo for therapeutic purposes. However, at the time of filing Treco (1995) stated, with regards to receptor mediated uptake of DNA for therapy that the method has promise but there are several major issues to resolved: undesirable uptake of DNA by non-target cells and non-specific uptake are the most relevant to present claims (page 318, col. 2, parag. 2, lines 1-6). Treco clearly indicates that while non-viral means for gene therapy were being developed at the time of filing, none had been shown to effectively overcome the lack of delivery and expression that plagued the field at that time.

Thus, at the time of the present invention, the skilled artisan would have needed to engage in an undue amount of experimentation without a predictable degree of success to achieve the scope of in vivo expression of a therapeutic protein.

Claims 1-9 and 17-48 are free of the art. At the time of filing the prior art did not teach or suggest methods of transfer using a transfer moiety of the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Reynolds, SPE of AU 1632 whose telephone number 703-305-4051. The examiner can normally be reached on M-Th.

Should inquiries be made on or after January 12, 2004, the examiner's phone number will be 571-272-0727. Deborah Reynolds will be reached at 571-272-0734.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306 for regular and After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

December 2, 2003